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(FILE 'HOME' ENTERED AT 11:43:06 ON 28 FEB 2001)

FILE 'MEDLINE, BIOSIS, SCISEARCH, EMBASE, CAPLUS' ENTERED AT 11:43:27 ON
28 FEB 2001

L1 2131122 S ANTIBODY
L2 284002 S L1 AND RECEPTOR
L3 11913 S L2 AND EPIDERMAL GROWTH FACTOR
L4 6 S L3 AND VEGF PRODUCTION
L5 0 S L4 AND INHIBIT

=> s l1 and EGFR

L6 2954 L1 AND EGFR

=> s l6 and VEGF production

L7 5 L6 AND VEGF PRODUCTION

=> dup remove

ENTER L# LIST OR (END):17

PROCESSING COMPLETED FOR L7

L8 1 DUP REMOVE L7. (4 DUPLICATES REMOVED)

=> d 18 all 1-4

L8 ANSWER 1 OF 1 MEDLINE DUPLICATE 1
AN 93184390 MEDLINE
DN 93184390
TI Epidermal growth factor stimulates vascular endothelial growth factor
production by human malignant glioma cells: a model of glioblastoma
multiforme pathophysiology.
AU Goldman C K; Kim J; Wong W L; King V; Brock T; Gillespie G Y
CS Brain Tumor Research Laboratories, Division of Neurosurgery, University
of Alabama, Birmingham 35294-0006.
NC T32NS07335 (NINDS)
NS31096 (NHLBI)
HL-41180
SO MOLECULAR BIOLOGY OF THE CELL, (1993 Jan) 4 (1) 121-33.
Journal code: BAU. ISSN: 1059-1524.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306
AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid
cellular proliferation are key histopathologic features of glioblastoma
multiforme (GBM), the most common and malignant of human brain tumors. By
immunoperoxidase and immunofluorescence, we definitively have
demonstrated
the presence of vascular endothelial growth factor (VEGF) and epidermal
growth factor receptor (EGFr) in five out of five human glioma
cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight
human GBM tumor surgical specimens. In vitro experiments with glioma cell
lines revealed a consistent and reliable relation between EGFr
activation and VEGF production; namely, EGF (1-20
ng/ml) stimulation of glioma cells resulted in a 25-125% increase in

secretion of bioactive VEGF. Conditioned media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca²⁺ ([Ca²⁺]i) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepared in the absence of EGF induced [Ca²⁺]i increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal antibody to VEGF, completely abolished VEGF-mediated [Ca²⁺]i transients in HUVECs. Likewise, induction by glioma-derived CM of von Willebrand factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation. Specifically, EGF activation of EGFR expressed on glioma cells leads to enhanced secretion of VEGF by glioma cells. VEGF released by glioma cells in situ most likely accounts for pathognomonic histopathologic and clinical features of GBM tumors in patients, including striking tumor angiogenesis,

increased cerebral edema and hypercoagulability manifesting as focal tumor

necrosis, deep vein thrombosis, or pulmonary embolism.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Brain Neoplasms: BS, blood supply

Brain Neoplasms: PA, pathology

Brain Neoplasms: PP, physiopathology

*Endothelial Growth Factors: BI, biosynthesis

*Epidermal Growth Factor: PD, pharmacology

Glioblastoma: BS, blood supply

Glioblastoma: PA, pathology

Glioblastoma: PP, physiopathology

*Glioma: ME, metabolism

Immunohistochemistry

*Lymphokines: BI, biosynthesis

Models, Biological

Neovascularization, Pathologic: PP, physiopathology

Receptor, Epidermal Growth Factor: ME, metabolism

Tumor Cells, Cultured: DE, drug effects

Tumor Cells, Cultured: ME, metabolism

RN 62229-50-9 (Epidermal Growth Factor)

CN EC 2.7.11.- (Receptor, Epidermal Growth Factor); O (vascular permeability factor); O (Endothelial Growth Factors); O (Lymphokines)

LA English
CC 14-1 (Mammalian Pathological Biochemistry)
Section cross-reference(s): 2
AB Hypervasularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathol. features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors.
By immunoperoxidase and immunofluorescence, we have definitively demonstrated the presence of vascular endothelial growth factor (VEGF) and **epidermal growth factor receptor** (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro expts. with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF** **prodn.**; namely, EGF (1-20 ng/mL) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF. Conditioned media (CM) prep'd. from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concns. of Ca²⁺ ([Ca²⁺]_i) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prep'd. in the absence of EGF induced [Ca²⁺]_i increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal **antibody** to VEGF, completely abolished VEGF-mediated [Ca²⁺]_i transients in HUVECs. Likewise, induction by glioma-derived CM of von Willebrand factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiolog. of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation.

Specifically, EGF activation of EGFr expressed on glioma cells leads to enhanced secretion of VEGF by glioma cells. VEGF released by glioma cells *in situ* most likely accounts for pathognomonic histopathol. and clin. features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein thrombosis, or pulmonary embolism.

ST EGF **receptor** vascular growth factor glioblastoma
IT **Receptors**
RL: BIOL (Biological study)
(**epidermal growth factor**, vascular endothelial growth factor formation stimulation by, in glioblastoma multiforme cells of humans)
IT Neuroglia
(neoplasm, glioblastoma multiforme, vascular endothelial growth factor formation in, **epidermal growth factor receptor** stimulation of, in human cells)
IT 127464-60-2, Vascular endothelial growth factor
RL: FORM (Formation, nonpreparative)
(formation of, by glioblastoma multiforme cells of humans, EGF **receptor** stimulation of)
IT 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(influx of, in human umbilical vein endothelial cells, vascular endothelial growth factor stimulation of, glioblastoma multiforme pathogenesis in relation to)
IT 62229-50-9, **Epidermal growth factor**
RL: BIOL (Biological study)
(**receptors** for, of glioblastoma multiforme cells of humans, vascular endothelial growth factor formation stimulation by)

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=> s antibody ..

L1 2131122 ANTIBODY

=> s l1 and receptor

L2 284002 L1 AND RECEPTOR

=> s l2 and epidermal growth factor

L3 11913 L2 AND EPIDERMAL GROWTH FACTOR

=> s l3 and VEGF production

L4 6 L3 AND VEGF PRODUCTION

=> s l4 and inhibit

L5 0 L4 AND INHIBIT

=> d l4 all 1-6

L4 ANSWER 1 OF 6 MEDLINE

AN 93184390 MEDLINE

DN 93184390

TI **Epidermal growth factor** stimulates vascular endothelial growth factor production by human malignant glioma cells: a model of glioblastoma multiforme pathophysiology.

AU Goldman C K; Kim J; Wong W L; King V; Brock T; Gillespie G Y

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CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

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- (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF production**; namely, EGF ($1-20 \text{ ng/ml}$) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF.
- Conditioned media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca^{2+} ($[\text{Ca}^{2+}]_i$) in human umbilical vein endothelial cells (HUVECs).
- Neither
- EGF alone or CM from glioma cultures prepared in the absence of EGF induced $[\text{Ca}^{2+}]_i$ increases in HUVECs. Preincubation of glioma CM with A4.6.1, a monoclonal **antibody** to VEGF, completely abolished VEGF-mediated $[\text{Ca}^{2+}]_i$ transients in HUVECs. Likewise, induction by glioma-derived CM of von Willebrand factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation.
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- CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
- Brain Neoplasms: BS, blood supply
- Brain Neoplasms: PA, pathology
- Brain Neoplasms: PP, physiopathology
- *Endothelial Growth Factors: BI, biosynthesis
- *Epidermal Growth Factor: PD, pharmacology
- Glioblastoma: BS, blood supply
- Glioblastoma: PA, pathology
- Glioblastoma: PP, physiopathology
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- Immunohistochemistry
- *Lymphokines: BI, biosynthesis
- Models, Biological
- Neovascularization, Pathologic: PP, physiopathology
- Receptor, Epidermal Growth Factor: ME, metabolism
- Tumor Cells, Cultured: DE, drug effects
- Tumor Cells, Cultured: ME, metabolism
- RN 62229-50-9 (Epidermal Growth Factor)
- CN EC 2.7.11.- (Receptor, Epidermal Growth Factor); 0 (vascular permeability factor); 0 (Endothelial Growth Factors); 0 (Lymphokines)
- L4 ANSWER 2 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1993:230726 BIOSIS
DN PREV199395121901
TI **Epidermal growth factor** stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology.
AU Goldman, Corey K. (1); Kim, Jin; Wong, Wai-Lee; King, Vickie; Brock, Tommy; Gillespie, G. Yancey (1)

CS (1) Brain Tumor Res. Lab., Div. Neurosurg., Dep. Surg., Univ. Ala.
Birmingham, Birmingham, AL 35294-0006

SO Molecular Biology of the Cell, (1993) Vol. 4, No. 1, pp. 121-133.
ISSN: 1059-1524.

DT Article

LA English

AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated the presence of vascular endothelial growth factor (VEGF) and **epidermal growth factor receptor** (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF production**; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF.

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CC Cytology and Cytochemistry - Human *02508
Clinical Biochemistry; General Methods and Applications 10006
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Metabolism - Minerals *13010
Metabolism - Proteins, Peptides and Amino Acids *13012
Cardiovascular System - Blood Vessel Pathology *14508
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Endocrine System - General *17002
Nervous System - Pathology *20506
Neoplasms and Neoplastic Agents - Pathology; Clinical Aspects; Systemic Effects *24004
Neoplasms and Neoplastic Agents - Neoplastic Cell Lines 24005
Neoplasms and Neoplastic Agents - Biochemistry *24006

BC Hominidae *86215

IT Major Concepts
Cardiovascular Medicine (Human Medicine, Medical Sciences); Cell Biology; Endocrine System (Chemical Coordination and Homeostasis); Hematology (Human Medicine, Medical Sciences); Metabolism; Neurology (Human Medicine, Medical Sciences); Oncology (Human Medicine, Medical Sciences)

IT Chemicals & Biochemicals
CALCIUM ION

IT Miscellaneous Descriptors
 CALCIUM ION CONCENTRATION; CH-235MG CELL LINE; D-54MG CELL LINE;
D-65MG
 CELL LINE; EMBOLISM; HYPERCOAGULABILITY; SURGICAL SPECIMENS;
 THROMBOSIS; TUMOR ANGIOGENESIS; U-105MG CELL LINE; U-251MG CELL LINE

ORGN Super Taxa
 Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
 Hominidae (Hominidae)

ORGN Organism Superterms
 animals; chordates; humans; mammals; primates; vertebrates

RN 14127-61-8 (CALCIUM ION)

L4 ANSWER 3 OF 6 SCISEARCH COPYRIGHT 2001 ISI (R)
AN 1998:167840 SCISEARCH
GA The Genuine Article (R) Number: YY117
TI Vascular endothelial growth factor induces heparin-binding
 epidermal growth factor-like growth factor in
 vascular endothelial cells
AU Arkonac B M (Reprint); Foster L C; Sibinga N E S; Patterson C; Lai K H;
 Tsai J C; Lee M E; Perrella M A; Haber E
CS HARVARD UNIV, SCH PUBL HLTH, CARDIOVASC BIOL LAB, 677 HUNTINGTON AVE,
 BOSTON, MA 02115 (Reprint); KAOHSIUNG MED COLL, DEPT MED, KAOHSIUNG,
 TAIWAN; HARVARD UNIV, SCH MED, DEPT MED, BOSTON, MA 02115; BRIGHAM &
 WOMENS HOSP, DIV PULM, BOSTON, MA 02115; BRIGHAM & WOMENS HOSP, DIV
 CARDIOVASC, BOSTON, MA 02115
CYA USA; TAIWAN
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (20 FEB 1998) Vol. 273, No. 8, pp.
 4400-4405.
 Publisher: AMER SOC BIOCHEMISTRY MOLECULAR BIOLOGY INC, 9650 ROCKVILLE
 PIKE, BETHESDA, MD 20814.
 ISSN: 0021-9258.
DT Article; Journal
FS LIFE
LA English
REC Reference Count: 50
AB Although several cytokines and growth factors have been shown to
 regulate vascular endothelial growth factor (**VEGF**)
 production, little is known about how VEGF may regulate growth
 factors that have known mitogenic and chemotactic actions on mesenchymal
 cells (which are involved in the maturation of the angiogenic process).
We
 investigated the effect of VEGF on heparin-binding **epidermal**
 growth factor-like growth factor (HB-EGF) expression in
 human umbilical vein endothelial cells. HB-EGF mRNA was induced by 8-fold
 after 2 h of VEGF stimulation, and it returned to base line within 6 h.
 VEGF did not alter the half-life of HB-EGF mRNA (55 min). Nuclear run-on
 experiments showed a 4.9-fold increase in HB-EGF gene transcription
within
 2 h of VEGF stimulation, and Western analysis demonstrated an associated
 increase in cellular HB-EGF protein. We found that platelet-derived
 growth
 factor-BB (PDGF-BB) mRNA was also induced 3-fold after 5 h of VEGF
 stimulation, whereas neither endothelin 1 nor transforming growth
 factor-beta 1 was regulated by VEGF. Finally, conditioned medium from
 VEGF-stimulated endothelial cells produced an increase in DNA synthesis
in
 vascular smooth muscle cells, and this effect was blocked by a
 neutralizing **antibody** to PDGF. The induction of HB-EGF and
 PDGF-BB expression in endothelial cells may represent the mechanism by
 which VEGF recruits mesenchymal cells to form the medial and adventitial
 layers of arterioles and venules during the course of angiogenesis.
CC BIOCHEMISTRY & MOLECULAR BIOLOGY

STP KeyWords Plus (R): SMOOTH-MUSCLE CELLS; FACTOR MESSENGER-RNA; FACTOR GENE;

ATHEROSCLEROTIC PLAQUES; RECEPTOR EXPRESSION; PHORBOL ESTER; ANGIOGENESIS; EGF; HYPOXIA; INDUCTION

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ALBERTS G F	1994	1269	10112	J BIOL CHEM
BERKMAN R A	1993	191	153	J CLIN INVEST
BLOCH K D	1989	1264	10851	J BIOL CHEM
BORNFELDT K E	1994	193	1266	J CLIN INVEST
BREIER G	1992	114	521	DEVELOPMENT
BROGI E	1994	190	1649	CIRCULATION
BROGI E	1996	197	1469	J CLIN INVEST
CARMELIET P	1996	1380	1435	NATURE
COHEN T	1996	1271	1736	J BIOL CHEM
CONNOLLY D T	1989	184	1470	J CLIN INVEST
DAMORE P A	1993	18	61	GROWTH FACTORS
DAMORE P A	1992	13	149	SEMIN CANCER BIOL
DAS S K	1994	120	1071	DEVELOPMENT
DVORAK H F	1995	146	1029	AM J PATHOL
FOLKMAN J	1996	187	1153	CELL
FOLKMAN J	1995	1333	1757	NEW ENGL J MED
FONG G H	1995	1376	166	NATURE
FREEMAN M R	1995	155	14140	CANCER RES
GIAID A	1995	159	R1308	TRANSPLANTATION
HANAHAN D	1996	186	1353	CELL
HIGASHIYAMA S	1992	1267	16205	J BIOL CHEM
HIGASHIYAMA S	1991	1251	1936	SCIENCE
KLAGSBRUN M	1993	13	699	CURR BIOL
KOOLWIJK P	1996	132	1177	J CELL BIOL
KUZUYA M	1995	164	1658	J CELL PHYSIOL
LAZAROUS D F	1996	194	1074	CIRCULATION
LEUNG D W	1989	1246	1306	SCIENCE
LEVY A P	1996	1271	12746	J BIOL CHEM
LI J	1995	1270	1308	J BIOL CHEM
LINDAHL P	1997	1277	1242	SCIENCE
MANDRIOTA S J	1995	1270	19709	J BIOL CHEM
MARIKOVSKY M	1993	190	13889	P NATL ACAD SCI USA
MIYAGAWA J	1995	195	1404	J CLIN INVEST
MORITA T	1993	1197	1256	BIOCHEM BIOPH RES CO
NEHLS V	1994	148	1349	MICROVASC RES
NEUFELD G	1994	15	189	PROG GROWTH FACTOR R
NICOSIA R F	1995	173	1658	LAB INVEST
NOMURA M	1995	1270	128316	J BIOL CHEM
O'BRIEN E R	1994	145	1883	AM J PATHOL
ORLIDGE A	1987	105	1455	J CELL BIOL
PATTERSON C	1995	1270	123111	J BIOL CHEM
PEPPER M S	1993	1204	1356	EXP CELL RES
PERRELLA M A	1994	1269	14595	J BIOL CHEM
RAAB G	1994	1204	1592	BIOCHEM BIOPH RES CO
RUEF J	1997	181	124	CIRC RES
SHALABY F	1995	1376	162	NATURE
SHWEIKI D	1992	1359	1843	NATURE
SURI C	1996	187	1171	CELL
TEMIZER D H	1992	1267	124892	J BIOL CHEM
YOSHIZUMI M	1992	1267	19467	J BIOL CHEM

L4 ANSWER 4 OF 6 SCISEARCH COPYRIGHT 2001 ISI (R)

AN 93:101700 SCISEARCH

GA The Genuine Article (R) Number: KM253

TI EPIDERMAL GROWTH-FACTOR STIMULATES VASCULAR

AU ENDOTHELIAL GROWTH-FACTOR PRODUCTION BY HUMAN-MALIGNANT GLIOMA-CELLS - A
CS MODEL OF GLIOBLASTOMA-MULTIFORME PATHOPHYSIOLOGY
Biol GOLDMAN C K (Reprint); KIM J; WONG W L; KING V; BROCK T; GILLESPIE G Y
 UNIV ALABAMA, DEPT SURG, DIV NEUROSURG, BRAIN TUMOR RES LABS, BIRMINGHAM,
 AL, 35294 (Reprint); UNIV ALABAMA, DEPT MED, DIV CARDIOVASC SCI, VASC
CYB & HYPERTENS PROGRAM, BIRMINGHAM, AL, 35294; GENENTECH INC, S SAN
 FRANCISCO, CA, 94080
SO MOLECULAR BIOLOGY OF THE CELL, (JAN 1993) Vol. 4, No. 1, pp. 121-133.
 ISSN: 1059-1524.
DT Article; Journal
FS LIFE
LA ENGLISH
REC Reference Count: 47
AB Hypervascularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated the presence of vascular endothelial growth factor (VEGF) and **epidermal growth factor receptor** (EGFr) in five out of five human glioma cell lines (U-251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF production**; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF.
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CC CYTOLOGY & HISTOLOGY; BIOCHEMISTRY & MOLECULAR BIOLOGY
STP KeyWords Plus (R): PERMEABILITY FACTOR; POSTOPERATIVE THROMBOEMBOLISM; NEUROSURGICAL PATIENTS; FACTOR-ALPHA; EXPRESSION; RECEPTOR; PROTEIN; ASTROCYTOMAS; PROGRESSION; POLYPEPTIDE
RE

Referenced Author (RAU)	Year (RPy)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ADACHI K	1992	34	370	CANCER IMMUNOL IMMUN
BAR R S	1989	124	1841	ENDOCRINOLOGY
BETHEA J R	1992	152	264	J CELL PHYSIOL
BETHEA J R	1990	30	1	J NEUROIMMUNOL
BETHEA J R	1992	36	179	J NEUROIMMUNOL
BIGNER D D	1981	40	210	J NEUROPATH EXP NEUR
BIGNER S H	1985	3	1769	NEUROL CLIN

BIGNER S H	1984	27	167	PROG EXP TUMOR RES
BLUMENSTOCK M	1991	11	11353	ANTICANCER RES
BOSTROM S	1986	80	183	ACTA NEUROCHIR
BOSTROM S	1987	88	149	ACTA NEUROCHIR
BRADY L W	1991	22	1225	INT J RADIAT ONCOL
BROCK T A	1991	138	1213	AM J PATHOL
BROCK T A	1988	136	154	J CELL PHYSL
BURGER P C	1987	57	11617	CANCER
BURGER P C	1989	63	12014	CANCER
CHEN T R	1977	104	1255	EXP CELL RES
CLAUSS M	1990	172	11535	J EXP MED
CONN G	1990	87	11323	P NATL ACAD SCI USA
CONNOLLY D T	1991	47	1219	J CELL BIOCHEM
CONSTANTINI S	1991	109	193	ACTA NEUROCHIR
CRISCUOLO G R	1989	71	1884	J NEUROSURG
FERRARA N	1991	47	1211	J CELL BIOCHEM
FETT J W	1985	24	15480	BIOCHEMISTRY-US
FOLKMAN J	1972	173	1409	ANN SURG
FULLING K H	1984	11	1152	SEMIN DIAGN PATHOL
GOSPODAROWICZ D	1987	8	195	ENDOCR REV
GOSPODAROWICZ D	1989	93	S 39	J INVEST DERMATOL
GRYNKIEWICZ G	1985	260	13440	J BIOL CHEM
HICKS C	1989	67	1271	IMMUNOL CELL BIOL
ISHIKAWA F	1989	338	1557	NATURE
KIM K J	1992	7	153	GROWTH FACTORS
LEUNG D W	1989	246	11306	SCIENCE
MARUNO M	1991	75	197	J NEUROSURG
MAXWELL M	1991	51	11345	CANCER RES
MONREAL M	1991	67	1541	CANCER
MURTHY U	1987	252	1549	ARCH BIOCHEM BIOPHYS
OHNISHI T	1991	10	113	J NEURO-ONCOL
PONTEN J	1968	74	1465	ACTA PATHOL MIC SC
PONTEN J	1978	56	1184	MED BIOL
ROBERTS A B	1986	84	14167	P NATL ACAD SCI USA
SANG U H	1989	74	183	J NEUROSURG
SCHREIBER A B	1986	232	11250	SCIENCE
TISCHER E	1991	266	111947	J BIOL CHEM
TUOMELA T	1990	46	11197	LIFE SCI
VIKSTRAND C J	1985	44	1229	J NEUROPATH EXP NEUR
ZAGZAG D	1990	50	17393	CANCER RES

L4 ANSWER 5 OF 6 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.

AN 93071308 EMBASE

DN 1993071308

TI **Epidermal growth factor** stimulates vascular endothelial growth factor production by human malignant glioma cells: A model of glioblastoma multiforme pathophysiology.

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SO Molecular Biology of the Cell, (1993) 4/1 (121-133).

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CY United States

DT Journal; Article

FS 005 General Pathology and Pathological Anatomy

016 Cancer

LA English

SL English

AB Hypervasularity, focal necrosis, persistent cerebral edema, and rapid cellular proliferation are key histopathologic features of glioblastoma multiforme (GBM), the most common and malignant of human brain tumors. By immunoperoxidase and immunofluorescence, we definitively have demonstrated

the presence of vascular endothelial growth factor (VEGF) and **epidermal growth factor receptor** (EGFr) in five out of five human glioma cell lines (U- 251MG, U-105MG, D-65MG, D-54MG, and CH-235MG) and in eight human GBM tumor surgical specimens. In vitro experiments with glioma cell lines revealed a consistent and reliable relation between EGFr activation and **VEGF production**; namely, EGF (1-20 ng/ml) stimulation of glioma cells resulted in a 25-125% increase in secretion of bioactive VEGF.

Conditioned

media (CM) prepared from EGF-stimulated glioma cell lines produced significant increases in cytosolic free intracellular concentrations of Ca²⁺ ([Ca²⁺]_i) in human umbilical vein endothelial cells (HUVECs). Neither EGF alone or CM from glioma cultures prepared in the absence of EGF induced [Ca²⁺]_i increases in HUVECs. Preincubation of glioma CM

with

A4.6.1, a monoclonal **antibody** to VEGF, completely abolished VEGF-mediated [Ca²⁺]_i transients in HUVECs. Likewise, induction by glioma-derived CM of von Willebrand factor release from HUVECs was completely blocked by A4.6.1 pretreatment. These observations provide a key link in understanding the basic cellular pathophysiology of GBM tumor angiogenesis, increased vascular permeability, and cellular proliferation.

Specifically, EGF activation of EGFr expressed on glioma cells leads to enhanced secretion of VEGF by glioma cells. VEGF released by glioma cells *in situ* most likely accounts for pathognomonic histopathologic and clinical features of GBM tumors in patients, including striking tumor angiogenesis, increased cerebral edema and hypercoagulability manifesting as focal tumor necrosis, deep vein thrombosis, or pulmonary embolism.

CT Medical Descriptors:

*angiogenesis
*glioblastoma
*glioma cell
*pathophysiology
adult
article
calcium cell level
cell proliferation
clinical feature
female
histopathology
human
human cell
tumor cell line

Drug Descriptors:

epidermal growth factor receptor
growth factor receptor
***epidermal growth factor**
*vasculotropin: EC, endogenous compound
(**epidermal growth factor**) 62229-50-9;
(vasculotropin) 127464-60-2

RN L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1993:210425 CAPLUS
DN 118:210425

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